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(54) **REPERTOIRE OF ALLO-RESTRICTED  
PEPTIDE-SPECIFIC T CELL RECEPTOR  
SEQUENCES AND USE THEREOF**

WO WO 2007/100568 A2 9/2007  
WO WO-2008/039818 A2 4/2008  
WO WO 2008/039818 A2 4/2008

**OTHER PUBLICATIONS**

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(58) **Field of Classification Search**  
None  
See application file for complete search history.

(56) **References Cited**

**U.S. PATENT DOCUMENTS**

4,703,004 A 10/1987 Hopp et al.  
4,851,341 A 7/1989 Hopp et al.  
5,906,936 A 5/1999 Eshhar et al.

**FOREIGN PATENT DOCUMENTS**

WO WO-97/32603 A1 9/1997  
WO WO 97/32603 A1 9/1997  
WO WO-2007/065957 A2 6/2007  
WO WO 2007/065957 A2 6/2007

Janeway et al., Immunobiology, 5th Ed., Garland Science, pp. 106-108 and 260-263, (2001).\*

Garcia et al., Cell, vol. 122, 333-336, Aug. 12, 2005.\*

Portolano et al., J Immunol. Feb. 1, 1993;150(3):880-7.\*

Dissertation of Elisa Kieback, Oct. 23, 2008, pp. 1-101.\*

The Memorandum from Deputy Commissioner for Patent Examination Policy Andrew H. Hirshfeld, dated Mar. 4, 2014, 19 pages in total with first page not numbered.\*

"Evaluating subject Matter Eligibility Under 35 U.S.C. § 101," Mar. 19, 2014 update, pp. 1-93.\*

Polic et al. (pnas, 8744-8749, Jul. 17, 2001, vol. 98, No. 15).\*

Roszkowski, J., et al., "Simultaneous Generation of CD8+ and CD4+ Melanoma-Reactive T Cells by Retroviral-Mediated Transfer of a Single T-Cell Receptor," *Cancer Research*, vol. 65(4), pp. 1570-1576 (Feb. 15, 2005).

Savage, P., et al., "Use of B cell-bound HLA-A2 class I monomers to generate high-avidity, allo-restricted CTLs against the leukemia-associated protein Wilms tumor antigen," *Blood*, vol. 103(12), pp. 4613-4615 (Jun. 15, 2004).

Javorovic et al., "Inhibitory effect of RNA pool complexity on stimulatory capacity of RNA-pulsed dendritic cells," *J Immunother.* 31(1):52-62 (2008).

Morgan et al., "Cancer regression in patients after transfer of genetically engineered lymphocytes," *Science* 314(5796): 10 pages (2006).

Morris et al., "Generation of tumor-specific T-cell therapies," *Blood Rev.* 20(2):61-9 (2006).

Roszkowski et al., "CD8-independent tumor cell recognition is a property of the T cell receptor and not the T cell," *J Immunol.* 170(5):2582-9 (2003).

Schumacher, "T-cell-receptor gene therapy," *Nat Rev Immunol.* 2(7):512-9 (2002).

Sommermeier et al., "Designer T cells by T cell receptor replacement," *Eur J Immunol.* 36(11):3052-9 (2006).

Sørensen et al., "A survivin specific T-cell clone from a breast cancer patient display universal tumor cell lysis," *Cancer Biol Ther.* 7(12):1885-7 (2008).

Visseren et al., "Affinity, specificity and T-cell-receptor diversity of melanoma-specific CTL generated in vitro against a single tyrosinase epitope," *Int J Cancer* 72(6):1122-8 (1997).

Wölfl et al., "Quantitation of MHC tetramer-positive cells from whole blood: evaluation of a single-platform, six-parameter flow cytometric method," *Cytometry A.* 57(2):120-130 (2004).

\* cited by examiner

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(57) **ABSTRACT**

The present invention is directed to a kit-of-parts or composition containing nucleic acid sequences coding for high-avidity, allo-restricted TCR, wherein the TCR are independently directed against the tyrosinase antigen, the melan-A antigen and the survivin antigen. The invention is further directed to a kit-of-parts or composition containing at least three groups of transgenic lymphocytes transformed with vectors coding for TCR against said antigens. Furthermore, the present invention provides a pharmaceutical composition and its use in the treatment of diseases involving malignant cells expressing said tumor-associated antigens. The invention further relates to a nucleic acid molecule coding for a TCR that recognizes the survivin antigen, a TCR encoded thereby and a T cell expressing said TCR. Further, the invention discloses a vector, a cell and a pharmaceutical composition encoding/containing same and their use in the treatment of diseases involving malignant cells expressing survivin.

**13 Claims, 3 Drawing Sheets**